AMENDMENTS TO THE DRAWINGS

The attached drawing sheet includes changes to Figure 5. Please note, the actual figure remains the same, however, that portion of the title referring to Antibody As Tracer, should read: (with PTH 1-[[8]]9 Antibody as Tracer).

Please replace Figure 5 with the presently submitted amended Figure 5.

Attachment: Replacement sheet

REMARKS

Paragraph **[0001]** of the present specification is amended to reflect the status of the two parent applications.

Figure 5 is amended to reflect the inventor's belief that PTH 1-9 antibody was used as a tracer antibody in the test results depicted in Figure 5. (*See* Exhibit 1., Cantor Decl.) The use of a PTH 1-9 antibody in a PTH assay is supported throughout the present application as originally filed, and *inter alia*, in paragraphs **[0014]** and **[0015]** of the present specification, Figure 2 and original claim 19.

Claims 1-83 were previously submitted for examination. Claims 1-9 and 60-80 were withdrawn from consideration, and claims 19-21 and 40-57 have been canceled. Claims 10, 25, 37, 59 and 81 are amended. New claims 84-90 are added. Therefore claims 10-18, 22-39, 58-59 and 81-90 are currently pending.

Support for the amended claims 10 and 59 can be found throughout the present application as originally filed, and *inter alia*, in paragraphs **[0014]** and **[0015]** of the present specification and in original claims 17-19. Support for the amended claim 25 can be found throughout the present application as originally filed and *inter alia*, in original claim 25. Claim 37 is amended to remove an incorrect abbreviation for the term "adynamic bone disease." Claim 81 is amended to remove an incorrect abbreviation for "picogram." Support for the amended claim 81 can be found throughout the present application as originally filed and *inter alia*, in paragraph **[0020]** of the present specification and in original claim 81. Support for the new claim 84 can be found throughout the present application as originally filed and *inter alia*, in paragraph **[0066]** of the present specification. Support for the new claim 85 can be found throughout the present application as originally filed and *inter alia*, in paragraphs **[0014]** and **[0015]** of the present specification and in original claims 17-19. Support for the amended claim 86 can be found throughout the present application as originally filed, and *inter alia*, in paragraphs **[00107]**, **[00134]** and **[00138]** of the present specification. Support for the new claims 87-90 can be found throughout the present application as originally filed and *inter alia*, in original claims 10, 17, 18 and 23.

According, the present amendments to the specification, drawings and claims do not add any new matter. Entry of the amendments is respectfully requested.

With respect to all amendments and canceled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Allowable Subject Matter

Applicant appreciates the Examiner's conclusion that claims 17-18 and 38-39 are allowable if rewritten in independent form. Applicant also appreciates the Examiner's diligence in reviewing the recently submitted Information Disclosure Statement and providing an initialed copy of it acknowledging consideration of the references disclosed therein.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claim 10 was rejected under 35 U.S.C. § 112, second paragraph, because the Examiner alleged that "it is not clear whether the method requires any label for determining the complex of wPTH and the antibody." Applicant traverses this rejection.

This rejection appears to relate only to the particular type of assay selected for the determination of the wPTH-antibody complex. However, the invention is not limited to a specific type of assay, and thus does not necessarily rely on a label. The list of assay formats discussed in the previous response, which was taken from paragraph **[0019]** of the specification, was intended to demonstrate that many different options are available in the art for assessing that complex. As the Examiner points out, some of these do not require labeling of the antibody or the antigenic wPTH

peptide. However, in view of the variety of methods mentioned, applicant should have pointed out that certain of the recited methods do not require a label at all.

For example, the present specification teaches:

> Alternatively, one could create an immunoassay in which PTH fragments are either precipitated from solution or otherwise differentiated in a solution, as in conventional precipitating assays or turbidometric assays. For example, one can use at least two or more antibodies to form a precipitating mass. These antibodies having specificity for N-terminal, C-terminal and/or mid-terminal portions of PTH. The combined mass of the PTH fragment and the antibodies would form a labeled precipitating mass which can be measured by conventional techniques.

(Paragraph **[00135]** of the present specification.) In this embodiment, none of the antibodies requires a label to generate a detectable signal.

Similarly, among the methods mentioned in paragraph **[0019]** is 'nephelometry', which involves measurement of the turbidity of a solution / suspension. (*See* the definition of Nephelometer in WEBSTER'S COLLEGIATE DICTIONARY, 10th ed. (1998): "an instrument for measuring the extent or degree of cloudniess..." Attached as Exhibit 2.) Turbidity develops when an antibody-antigen complex becomes large enough to precipitate from the medium under the operating conditions. A turbidometric assay depends upon the concentration of the complex and its solubility in the solution; it thus does not require addition of a label to either component of the complex, nor does it require a label on a separate component such as an enzyme substrate. The specification again mentions such "conventional precipitating assays or turbidometric assays" at paragraph **[00108]**. In that context, it indicates that a third antibody can be used to induce precipitation of the wPTH-antibody complex. These methods are based on physical phenomena involving only the complex between antibodies and a PTH peptide; they do not require anything that would be considered a 'label' as that term is ordinarily used. Thus the methods and kits as claimed and described can be practiced without a label. Adding a limitation to the claim requiring the use of a label would therefore unduly limit the scope of the invention as it is described in the application.

Further, binding of a whole PTH to an antibody would lead to the formation of a PTH/antibody complex. Since the sequence, and the hence the molecular weight, of a whole PTH is known, the complex would have a molecular weight increase due to the addition of the whole PTH molecule. Mass spectrometry, a well know detection technique, is capable of detecting molecular weight changes. Therefore, binding of the whole PTH to the antibody can be detected by mass spectrometry without using any label in the method.

Claim 25 was also rejected under 35 U.S.C. § 112, second paragraph; the Examiner stated that "it is not clear what is the relationship of this second antibody to the first antibody." The claim as examined said this:

"25. The method of claim 24, wherein the antibody that specifically binds to an N-terminal sequence of whole PTH is used as a first antibody and an antibody that is capable of binding to a portion of whole PTH other than the N-terminal sequence which binds to the first antibody is used as a second antibody in a sandwich assay format."

The wording of this claim led the Examiner to interpret it to say that "the first antibody binds to the second antibody." This interpretation made the claim allegedly inconsistent with certain of the Figures in the application.

Applicant traverses this rejection, and believes the claim as drafted clearly indicated that the second antibody is one that "is capable of binding to a portion of whole PTH other than the N-terminal sequence which binds to the first antibody..." The claim did not intend to convey binding of the second antibody to the first antibody. However, to enhance clarity and advance prosecution, that claim has been amended. It now says:

"25. The method of claim 24, wherein the antibody that specifically binds to an N-terminal sequence of whole PTH is used as a first antibody in a sandwich format assay, and a second antibody used in the sandwich format assay is an antibody that is capable of binding to a portion of whole PTH other than the N-terminal sequence to which the first antibody binds."

This amendment is intended only to clarify the claim and not to change its scope. The amended claim believed to be fully consistent with the Figures and with the assay as described in the specification. Therefore, applicant requests that this rejection be withdrawn in light of the amendment to claim 25.

This rejection was applied to claims 10-18, 22-39, 58-59 and 81-83, apparently only due to their dependence from claim 10 or claim 25. In light of the above amendments and comments, applicant therefore requests the withdrawal of this rejection for all applicable claims.

Rejections under 35 U.S.C. § 102

Claims 10-16, 22-37, 58 and 81-83 were rejected under 35 U.S.C. 102(b) as allegedly unpatentable over Gao, et al. (*Clinica Chimica Acta* 245, 39-59 (1996)). According to the Examiner, Gao discloses "antibodies specific for the N-terminal, but not able to bind to the non-whole PTH fragments such as 4-16, 28-48, 39-84 and 53-84." These antibodies allegedly distinguished wPTH from at least some non-whole PTH fragments. Methods of using these antibodies to detect hPTH were allegedly disclosed as well.

Applicant respectfully traverses this rejection. However, in order to advance the prosecution, applicant has amended claims 10 and 59, which now recite "said isolated antibody specifically binds to an epitope comprised in PTH_{1-5}, PTH_{1-6}, PTH_{1-7}, PTH_{1-8}, PTH_{1-9}, PTH_{1-10}, PTH_{1-11}, PTH_{1-12}, PTH_{1-13}, PTH_{1-14} or PTH_{1-15}" As recognized by the Examiner in indicating the allowability of claims 17 and 18, Gao does not disclose using antibodies specifically for the epitopes comprised in PTH_{1-6}, PTH_{1-8}, PTH_{1-9}, PTH_{1-12}, or PTH_{1-15}. Gao also does not disclose using antibodies specifically for the epitopes comprised in epitopes comprised in PTH_{1-5}, PTH_{1-7}, PTH_{1-10}, PTH_{1-11}, PTH_{1-13} or PTH_{1-14}.

In addition, claim 23 further requires that the non-whole PTH fragment to be avoided in the assay is a peptide having an amino acid sequence of human PTH_{7-84}. Gao compared its PTH

assay with the Allegro intact PTH assay from Nichols Institute Diagnostics. (Gao at pages 42-43.) Gao states:

> The comparison with the intact PTH assay is shown in Fig. 4; samples from 32 normal subjects, 29 patients with primary hyperparathyroidism and 45 hemodialysis patients were determined with both this new PTH sandwich assay and the intact PTH sandwich assay. We obtained a good agreement between the two assays in normal volunteers and in primary hyperparathyroidism, and an excellent correlation in dialysis patients with a regression slope of 1.8.

(Gao at page 48.)

The present specification further teaches:

> Initial studies compared the ability of the Nichols Intact (I-Nichols) PTH assay and the new Whole PTH assay to discriminate between the hPTH 1-84 and hPTH 7-84 molecules. Figure 13 shows that the Nichols "intact" PTH assay did not discriminate between human PTH 1-84 and 7-84. However, as depicted in Figure 14, studies performed using the Whole PTH assay show that hPTH 1-84 was detected with a high degree of sensitivity, whereas hPTH 7-84 was undetectable, even at a concentration as high as 10,000 pg/mL.

(The present specification at paragraph **[00154]** on page 45.)

Nichols Intact (I-Nichols) PTH assay is not capable of discriminating between the hPTH 1-84 and hPTH 7-84 molecules as shown in Figure 13 of the present specification. Since Gao's PTH assay correlates with Nichols Intact PTH assay, Gao's PTH assay is not capable of discriminating between the hPTH 1-84 and hPTH 7-84 molecules as well. Therefore, Gao does not anticipate claim 23 for this additional reason.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. §102.

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 532212000623. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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